Remarks

The August 11, 2003 Official Action has been carefully reviewed. In view of the amendments submitted herewith and these remarks, favorable reconsideration and allowance of this application are respectfully requested.

At the outset it is noted that a shortened statutory response period of three (3) months was set forth in the August 11, 2003 Official Action. The initial due date for response, therefore, was November 11, 2003. A petition for a one month extension of the response period is presented with this response, which is being filed within the one month extension period.

In the August 11, 2003 Official Action, the Examiner notes that the application does not fully comply with the requirements of 37 C.F.R. §§1.821-1.825.

It is also the Examiner's position that claims 1, 4, 6, and 8-10 may not receive the benefit of an earlier filing date under 35 U.S.C. §120 because the claims recite a "conjugated thiol" which is allegedly new matter. Therefore, claims 1, 4, 6, and 8-10 have been afforded the filing date of the instant application (7/12/01).

The Examiner has objected to claims 1, 4, 6, and 8-10 for reciting the term "conjugated thiol" which allegedly lacks antecedent basis within the specification.

Additionally, the Examiner has rejected claims 1-11 under 35 U.S.C. §112, second paragraph as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. The Examiner considers the claim language deficient in several respects, as indicated in the paragraph bridging pages 3-4 of the August 11 Official Action.

The Examiner has also rejected claims 1, 4, 6, and 8-10 for allegedly failing to satisfy the written description requirement under 35 U.S.C. §112, first paragraph. The Examiner alleges the term "conjugated thiol" is not defined in

the specification.

Claims 1, 4, 6, 8, and 10 are also rejected under 35 U.S.C. §102(a,b) as allegedly anticipated by Severinov et al. (J. Biol. Chem. (1998) 273:16205-16209). Serevinov et al. allegedly teach a method of ligating an expressed protein with a peptide in the presence of the "conjugated thiol" thiophenol.

The Examiner has also rejected claims 1, 4, 6, 8, and 9 under 35 U.S.C. §103 (a) as allegedly unpatentable over U.S. Patent No. 5,834,247 and Dawson et al. (Science (1994) 266:776-779). Additionally, claims 1-9 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. Patent No. 5,834,247 and Dawson et al. (1994) in view of WO 96/34878 and/or Dawson et al. (J. Amer. Chem. Soc. (1997) 119:4325-4329). Claims 1-11 stand rejected as allegedly unpatentable over U.S. Patent No. 5,834,247 and Dawson et al. (1994) in view of WO 96/34878 and/or Dawson et al. (1997) and further in view of Chong et al. (Gene (1997) 192:271-281).

Lastly, claims 1-11 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-11 of copending Application No. 09/879,744.

The foregoing objections and rejections constitute all of the grounds set forth in the August 11, 2003 Official Action for refusing the present application.

In accordance with the present amendments, the specification has been amended to provide appropriate sequence identifiers throughout. These amendments are believed to place the application in full compliance with 37 C.F.R. §§1.821-1.825. Furthermore, claim 1 has been amended so that the wording "Recombinantly expressed protein" is used consistently throughout. Claim 1 has been further amended to call for formation of an amide bond "linking the C-terminus of said protein to the N-terminus of said peptide.

Also presented with the amendment is a new claim 12, which is directed to the embodiment of the invention

summarized at page 7 lines 9-12 of the specification.

No new matter has been introduced into this application by reason of any of the amendments presented herewith. Moreover, none of the present claim amendments is believed to constitute a surrender of any originally claimed subject matter, or a narrowing of the claims in order to establish patentability. The effect of these amendments is merely to make explicit that which was implicit in the claims as originally worded.

CLAIM 1, AS AMENDED, AND CLAIMS 2-11 FULLY SATISFY THE REQUIREMENTS OF 35 U.S.C. 112, SECOND PARAGRAPH

In support of the 35 U.S.C. §112, second paragraph rejection of claims 1-11 the Examiner asserts that claim 1 is unclear due to the use of the phrase "conjugated thiophenol." It is the Examiner's position that it is unclear how a "conjugated thiophenol" can encompass benzoic and pyridine compounds present in the Markush group of claim 2. Additionally, claim 1 allegedly lacks antecedent basis for the phrase "said bound recombinant protein." Lastly, the Examiner alleges essential steps are omitted from claim 1, with specific reference to ligation of the peptides "end to end" and the absence of a step effecting the "said bound recombinant protein."

Applicants respectfully submit that none of the claims recite the term "conjugated thiophenol" as asserted by the Examiner. Accordingly, claim 1 and dependent claims therefrom cannot properly be considered indefinite for this reason.

Similarly, the rejection of claim 2 because of the ambiguity perceived by the Examiner as to how a "conjugated thiophenol" can encompass benzoic and pyridine compounds recited in the Markush group of claim 2 is improper because claim 2 fails to recite the allegedly ambiguous term "conjugated thiophenol." Indeed, claim 2 recites a

"conjugated thiol." Inasmuch as the term "conjugated" in organic chemistry refers to compounds comprising double bonds that alternate with single bonds, Applicants submit that a skilled artisan would readily appreciate that a "conjugated thiol" can encompass benzoic and pyridine compounds.

Applicants have amended claim 1 to replace the phrase "said bound recombinant protein" with "said recombinantly expressed protein bound to an intein-CBD" which has antecedent basis within the claim. Applicants have also amended claim 1 to recite that the claimed method results in the ligation of "the C-terminus of said protein with the N-terminus of said peptide" and thus denoting that ligation of the peptide and protein occurs end-to-end.

In light of the foregoing, Applicants respectfully submit that claim 1, as amended, and claims 2-11 all meet the requirements of 35 U.S.C. §112, second paragraph.

CLAIM 1, AS AMENDED, AND CLAIMS 4, 6, AND 8-10 FULLY SATISFY THE WRITTEN DESCRIPTION REQUIREMENT OF 35 U.S.C. 112, FIRST PARAGRAPH AND THE TERM "CONJUGATED THIOL" HAS ANTECEDENT BASIS WITHIN THE SPECIFICATION AND PARENT APPLICATIONS

The Examiner contends in support of this ground of rejection that the metes and bounds of term "conjugated thiol" are unclear. For the reasons set forth above, Applicants respectfully submit that a skilled artisan would readily recognize whether or not a given compound qualifies as a "conjugated thiol."

As noted above, the term "conjugated," in organic chemistry, refers to compounds comprising double bonds that alternate with single bonds. Therefore, a "conjugated thiol" would include compounds which contain a thiol attached to a structure which comprises double bonds that alternate with single bonds, such as in benzene and pyridine structures. Furthermore, Applicants have provided a list of representative "conjugated thiols" at page 22, lines 5 through 7 which meet

these requirements. Inasmuch as the meaning of "conjugated thiol" would be readily understood by a skilled artisan and given that a list of representative examples of "conjugated thiols" is provided in the specification, Applicants submit that the specification meets the written description requirement of 35 U.S.C. 112, first paragraph. Accordingly, this ground of rejection should be withdrawn.

Applicants take exception to the Examiner's contention that the thiophenol structure is critical to the successful practice of the instant invention. In this connection the Examiner's attention is respectfully directed to the statement at page 24, lines 20-23 identifying thiophenol as the "only co-factor tested" to support efficient cleavage and ligation. It is clear when properly considered in context that this statement refers only to the group of tested co-factors mentioned in the previous paragraph, i.e. DTT, N-acetyl cysteine, cysteine, mercaptoacetic acid, and thiophenol. Of the listed co-factors, only thiophenol can be considered a "conjugated thiol."

Furthermore, the disclosure of "conjugated thiol" at page 22, lines 5 through 7 of the present specification plainly refutes the Examiner's contention that this term lacks antecedent basis within the specification.

Additionally, it is noted that the term "conjugated thiol" is also employed throughout the parent applications (see, e.g., page 22, lines 5 through 7 of U.S. Patent Application No. 09/191,890 and page 7, lines 14-16 of U.S. Provisional Application 60/065,391). Inasmuch as the same definition and examples are provided throughout the parent applications as in the instant application, Applicants contend that the term is described in sufficient detail to satisfy the requirements of 35 U.S.C. §112, first paragraph and the filing date of the provisional application (November 13, 1997) should be afforded as the priority date of the instant application.

CLAIMS 1, 4, 6, 8, AND 10 ARE NOT ANTICIPATED BY SEVERINOV ET AL.

The Examiner has rejected claims 1, 4, 6, 8, and 10 under 35 U.S.C. §102(a,b) as allegedly lacking novelty over the disclosure in Severinov et al.

The Examiner has afforded only the filing date of the instant application (July 12, 2001) for claims 1, 4, 6, 8, and 10, thereby allowing Severinov et al. (published June 1998) to be cited as prior art. As stated hereinabove, the claimed invention should rightfully be given the priority date of the filing of the provisional application (November 13, 1997) as the term "conjugated thiol" is not new matter. Inasmuch as the proper priority date of the claimed invention is prior to the date of the Severinov et al. publication, the rejection under 35 U.S.C. §102(a,b) is untenable and should be withdrawn.

Before addressing the various rejections under §103, it is noted that the Examiner is correct in assuming at page 8 of the August 11, 2003 Official Action, that the subject matter of the various claims was commonly owner at the time the invention covered thereby was made.

CLAIMS 1, 4, 6, 8, AND 9 ARE NOT OBVIOUS IN VIEW OF U.S. PATENT 5,834,247 AND DAWSON ET AL. (1994)

In support of the 35 U.S.C. §103(a) rejection of claims 1, 4, 6, 8, and 9, the Examiner contends that U.S. Patent 5,834,247 discloses a method of cleaving an intein-chitin binding domain (intein-CBD) from an expressed protein and ligating a peptide containing an N-terminal cysteine by incubating the peptide with the expressed protein in the presence of a thiol. The Examiner submits, however, that U.S. Patent 5,834,247 fails to explicitly teach the presence of a "conjugated thiol" to promote ligation. The Examiner notes that U.S. Patent 5,834,247 references the chemical ligation technique disclosed in Dawson et al. (1994) which allegedly employs benzyl mercaptan to effect chemical ligation.

Applicants submit that nowhere in U.S. Patent 5,834,247 is there disclosure of a method for ligating a protein bound to an intein-CBD to a peptide containing an N-terminal cysteine in the **presence of a thiol**. Indeed, the only disclosures in U.S. Patent 5,834,247 of directly ligating a protein and a peptide are the broad descriptions at column 7, lines 27-29; column 75, lines 53-58; and at column 77, lines 57-58. These citations merely mention that a labeled cysteine, which includes peptides with an N-terminal cysteine, can be "used to induce the cleavage reaction resulting in the attachment of the labeled molecule to the C-terminus of the target protein." There is no mention of performing the reaction in the presence of a thiol.

Notably, U.S. Patent 5,834,247 discloses, as an alternative, that the labeled cysteine can be "added to a protein sample **following** a thiol-induced cleavage reaction" (column 77, lines 57-60). Moreover, Example 19 of U.S. Patent 5,834,247 provides examples of this alternative method of first treating with a thiol and then a labeled cysteine. The method involves utilizing the thiol-containing compound DTT to cleave the protein bound to an intein-CBD and then **isolating** the resultant cleavage product prior to incubation with a peptide containing an N-terminal cysteine (see column 76, lines 26-35). Due, in part, to the purification of the cleavage product, this method is not performed in a "single pot" as asserted by the Examiner.

The Examiner also cites Figure 28, Example 15 and claims 96-103 of U.S. Patent 5,834,247 to support the assertion that U.S. Patent 5,834,247 discloses a method of ligating a protein and a peptide in the presence of a thiol. Applicants submit that Example 15 describes only the production of the intein-chitin binding domain containing proteins. Additionally, Figure 28 and claims 96-103 are silent as to including a conjugated thiol in order to promote the cleavage and ligation reactions. In fact, claims 98 and

99 specifically recite that the labeled cysteine is added only **after** the treatment of the fusion protein with a thiol compound.

Therefore, U.S. Patent 5,834,247 fails to disclose or suggest a method for ligating a protein and a peptide in the presence of a thiol as asserted by the Examiner.

The Examiner also asserts, in support of the obviousness rejection, that Dawson et al. (1994) teach the use of benzyl mercaptan "to effect chemical ligation." Applicants submit, however, that nowhere in Dawson et al. is the purpose of the presence of benzyl mercaptan disclosed. Indeed, the only mention of benzyl mercaptan is in footnote 30, wherein the compound is simply listed as one of several compounds in the reaction buffer. Based on the teachings of Dawson et al. (1994), a skilled artisan would have no reason to suspect that the benzyl mercaptan was critical to the ligation of the two polypeptides. Indeed, a skilled artisan may readily come to the conclusion that because the thioester containing peptide in the reaction possessed a benzyl "leaving group" attached to the thioester, the benzyl mercaptan was provided in the reaction medium in order to establish an equilibrium wherein the benzyl group remained on the peptide (e.g., to counteract hydrolysis). Inasmuch as the instantly claimed method employs a protein bound to an intein-chitin binding domain as opposed to an alkyl group that acts as a leaving group, a skilled artisan, based on the teachings of Dawson et al. (1994), would not come to the conclusion that benzyl mercaptan or any "conjugated thiol" would be useful or required in the ligation of the protein with a peptide.

Furthermore, it is a well-settled principle of patent law that "silence in a reference is not a proper substitute for adequate disclosure of facts from which a conclusion of obviousness may justifiably follow". In re Burt, 148 U.S.P.Q. 548 (CCPA 1966). Clearly, the silence in Dawson et al. (1994) as to any significance of, or purpose for the

inclusion of benzyl mercaptan in the reaction buffer fails to provide any motivation to a skilled artisan to employ a conjugated thiol in the ligation scheme described in U.S. Patent No. 5,834,247.

Accordingly, the 35 U.S.C. §103(a) rejection of claims 1, 4, 6, 8, and 9 based on U.S. Patent 5,834,247 and Dawson et al. (1994) is improper and should be withdrawn.

THE COMBINED DISCLOSURES OF U.S. PATENT 5,834,247 DAWSON ET AL. (1994), WO 96/34878 AND/OR DAWSON ET AL. (1997) FAIL TO RENDER CLAIMS 1-9 OBVIOUS

The Examiner contends that WO 96/34878 and Dawson et al. (1997) teach the advantages of using "conjugated thiols," including thiophenol, in the chemical ligation of peptides. Specifically, the Examiner cites pages 7 and 14, claims 1-7 and the examples of WO 96/34878 in support of the desirability of employing conjugated thiols in the ligation of peptides.

Applicants submit, however, that the peptides of WO 96/34878 differ significantly from those of the instant invention. Notably, the thioester containing peptide described in WO 96/34878 is chemically synthesized and contains an "alkyl group such as benzyl, 5-thio-2-nitrobenzoic acid, thiophenol, etc." as part of the thioester as a leaving group (page 27, lines 24-25). However, the thioester containing protein of the instant invention, which contains an intein-chitin binding domain attached to the thioester, is a relatively stable derivative and not an alkyl leaving group as described in WO 96/34878. Therefore, Applicants submit that a skilled artisan would not have had a reasonable expectation of success in employing the conjugated thiols of WO 96/34878 to effect the cleavage and ligation of a recombinant protein bound by an intein-chitin binding domain and a peptide containing an N-terminal cysteine.

Similarly, Dawson et al. (1997) merely teaches the exchange of various alkyl groups (e.g., benzyl) attached to

the thioester group and the ability of thiophenol to increase the reaction rate between an αCOS-benzyl containing peptide and a peptide containing an N-terminal cysteine. Dawson et al. is silent, however, as to the ability of conjugated thiols to effect the cleavage and ligation reactions of a thioester located between a recombinant protein and an intein-chitin binding domain, as required in the instant claims.

Inasmuch as WO 96/34878 and Dawson et al. are silent as to any advantage conjugated thiols may impart to the cleavage and ligation of a thioester as a stable derivative with an intein-chitin binding domain as opposed to a alkyl leaving group, the rejection of claims 1-9 under 35 U.S.C. §103 is improper and should be withdrawn.

CLAIMS 1-11 ARE NOT OBVIOUS OVER U.S. PATENT 5,834,247 AND DAWSON ET AL. (1994) IN VIEW OF WO 96/34878 AND/OR DAWSON ET AL. (1997) AND FURTHER IN VIEW OF CHONG ET AL.

In support of this obviousness rejection, the Examiner further cites Chong et al. which allegedly describes employing the pCYB vector, claimed in claims 10 and 11, to make the recombinant proteins bound to an intein-chitin binding domain.

Inasmuch as the primary references cited in support of this rejection fail to render obvious the claimed method, as set forth above, it necessarily follows that claims 10 and 11 are non-obvious, regardless of whether Chong et al. teaches the pCYB vectors of the instant invention. Therefore, Applicants respectfully request the withdrawal of this rejection.

THE OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTION OF CLAIMS 1-11 IS UNTENABLE IN VIEW OF THE ABANDONMENT OF THE '744 APPLICATION

It is hereby requested that this obviousness type double patenting rejection be withdrawn as moot in view of the

abandonment of the '744 application on which this rejection is based.

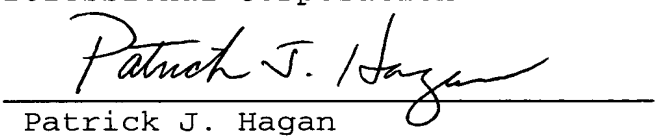
CONCLUSION

In view of the amendments presented herewith and the foregoing remarks, it is respectfully urged that the objections and rejections set forth in the August 11, 2003 Official Action be withdrawn and that this application be passed to issue.

In the event the Examiner is not persuaded as to the allowability of any claim, and it appears that any outstanding issues may be resolved through a telephone interview, the Examiner is requested to telephone the undersigned attorney at the phone number given below.

Respectfully submitted,

DANN, DORFMAN, HERRELL AND SKILLMAN
A Professional Corporation

By 

Patrick J. Hagan
PTO Registration No. 27,643

Telephone: (215) 563-4100
Facsimile: (215) 563-4044